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Studies on the Heterocyclic Compounds. XIX.[1] A Novel Ring Isomerization of 3-Ylideneaminoimidazo[4,5-*c*]pyridazines

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Several 3-ylideneaminoimidazo[4,5-*c*]pyridazines (IV and VI) were synthesized for the investigation of the ring isomerization reaction. The reactions of IVa, IVb, IVc, and IVd with 5% or 50% acetic acid gave VIII as the ring isomerization product. Similarly IVe afforded X. In the case of IVd, intermediate product (IXd) was obtained by the reaction with 50% acetic acid. This compound (IXd) was converted to VIII by the treatment with 70% acetic acid. The possible reaction mechanism was proposed.

During the investigation of hydrolysis of 3-benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine[3] (IVa) with 1N hydrochloric acid, it was found that IVa was converted into 6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine (VIII) as ring isomerization product.[4] In this paper, we report further investigations of the ring isomerization reaction which include carbon migration.

Syntheses of 3-Ylideneaminoimidazo[4,5-*c*]pyridazines

3-Hydrazino-4-amino-6-chloropyridazine (I) was condensed with acetone, benzaldehyde, *p*-methyl-, *p*-methoxy-, and *p*-nitrobenzaldehyde to obtain the corresponding 3-ylidenehydrazino derivatives (II and V). In the cases of *p*-methyl- and *p*-methoxybenzaldehyde, cyclization products (IIIb and IIIc) were also obtained from the mother liquor of recrystallization of II, respectively. These products were established to 3-(*p*-methyl- and *p*-methoxyphenyl)-6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazines by comparison of ultraviolet (UV) spectra with that of 3-phenyl-6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine[3] (IIIa). When sodium nitrite was added to a mixture of IIc and 30% acetic acid, the same cyclization product (IIIc) was obtained under mild reaction condition.

Cyclizations of II and V afforded the corresponding 3-ylideneaminoimidazo[4,5-*c*]pyridazines (IV and VI) by the reaction with ethyl orthoformate, respectively. When V was treated with a mixture of ethyl orthoformate and *N*,*N*-dimethylformamide, a different compound (VII) was obtained. This compound had a melting point of 216° and elementary analysis was equivalent to $C_5H_4N_5Cl$. The UV spectrum of this compound was similar to that of imidazo[4,5-*c*]pyridazine derivatives[3,5] and nuclear magnetic resonance (NMR) spectrum showed three singlet peaks at 8.76 ppm (1H), 8.20 ppm (1H), and 6.43 ppm (2H, disappear by addition of D_2O). The former two peaks were assignable to ring protons of 2 and 7 position by comparison of NMR spectra of imidazo[4,5-*c*]pyridazine (8.89 ppm (1H, 2 position), 8.13 ppm (1H, 7 position)) and the later was assignable to primary amino group. The compound VII was presumed to be 3-amino-6-chloroimidazo[4,5-*c*]pyridazine which was an important compound for solution of reaction mechanism of the ring isomerization reaction. The reaction

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[1] Part XVIII: M. Yanai, S. Takeda, T. Baba, and K. Kitagawa, *Yakugaku Zasshi*, **94**, 1503 (1974).

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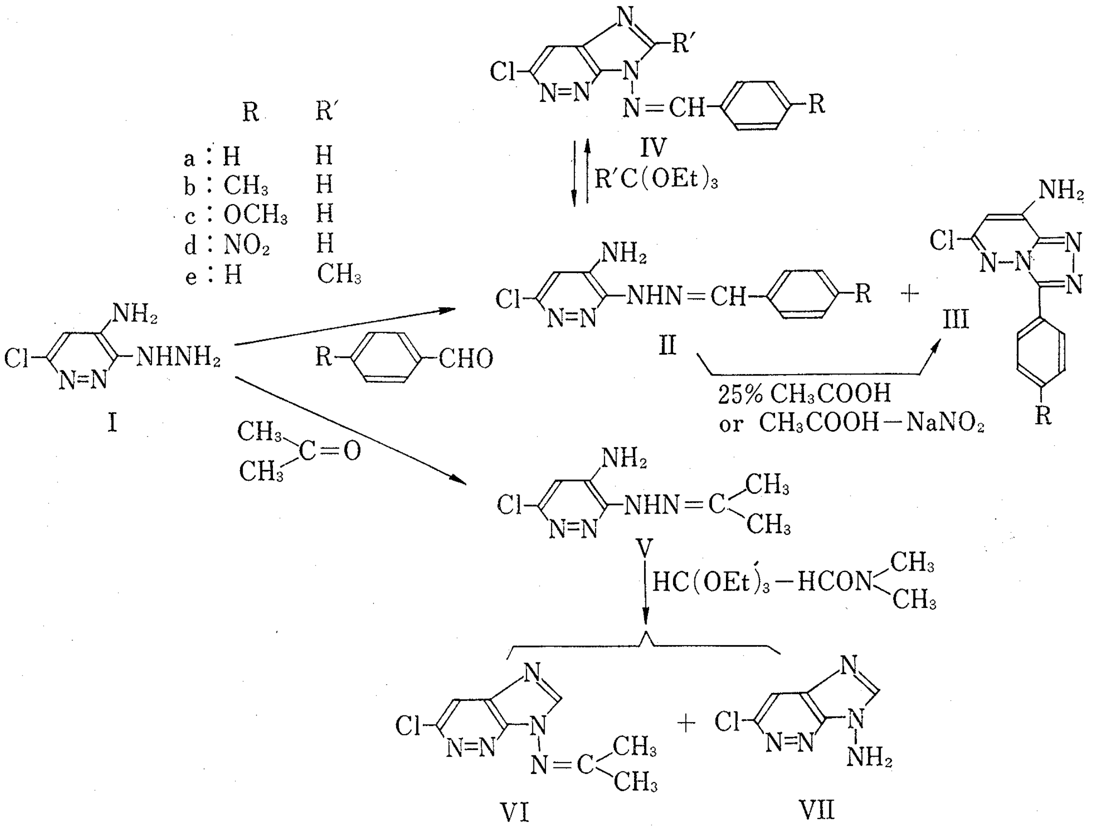
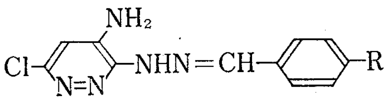
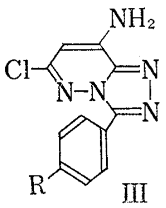
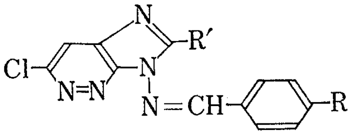


Chart 1

Table I. Yields and Elemental Analyses of II, III and IV


II


III


IV

Compound No.	R	R′	Appearance	mp (°C)	Yield (%)	Recryst. solvent	Formula	Anal. Calcd./Found (%) C	H	N
IIb	CH_3	—	colorless flakes	217—219	65	EtOH	$C_{12}H_{12}N_5Cl$	55.07 55.24	4.62 4.84	26.76 26.57
IIc	OCH_3	—	colorless flakes	220—221	90	MeOH	$C_{12}H_{12}ON_5Cl$	51.90 52.23	4.36 4.55	25.22 25.01
IId	NO_2	—	Reddish cubes	262—264	90	pyridine	$C_{11}H_9O_2N_6Cl$	45.14 45.18	3.10 3.22	28.71 28.54
IIIb	CH_3	—	colorless needles	272—273	—	MeOH	$C_{12}H_{10}N_5Cl$	55.50 55.29	3.88 4.10	26.97 26.56
IIIc	OCH_3	—	colorless prismes	283—284	—	MeOH	$C_{12}H_{10}ON_5Cl$	52.28 52.21	3.66 3.63	25.40 25.54
IVb	CH_3	H	colorless needles	174—175	50	acetone	$C_{13}H_{10}N_5Cl$	57.47 57.77	3.71 3.92	25.78 25.45
IVc	OCH_3	H	colorless needles	209—210	70	MeOH	$C_{13}H_{10}ON_5Cl$	54.27 54.38	3.50 3.62	24.34 23.79
IVd	NO_2	H	orange powderes	260—262	90	pyridine	$C_{12}H_7O_2N_6Cl$	47.62 47.71	2.33 2.26	27.77 26.59
IVe	H	CH_3	colorless needles	208—209	59	MeOH	$C_{13}H_{10}N_5Cl$	57.47 57.32	3.71 3.72	25.78 25.48

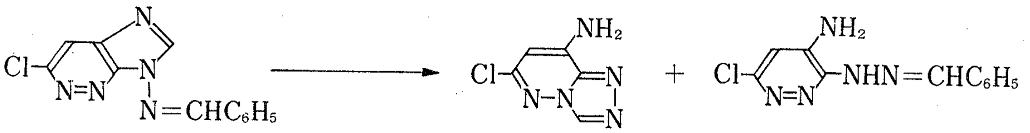
were tried several times under the same and various conditions, however we could not raise the yield of VII.

Reaction of 3-Ylideneaminoimidazo[4,5-*c*]pyridazines (IV) with Acids

First 3-benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (IVa) was treated with several kinds of acidic solution. These results are summarized in Table II. When hydrochloric acid was used as reagent, the ring isomerization product (VIII) was obtained more than a ring opening product (IIa). However, the yield of VIII was reduced according to the dilution of the acid. If we use acetic acid instead of hydrochloric acid, the ring isomerization becomes predominant and thus IVa was converted into VIII in 91% yield by the reaction with 5% acetic acid. The treatment of IVa with 50% acetic acid or a solution of three drops of acetic acid and 20 ml of water gave VIII in 70% or 76% yield, respectively. When IVa was treated with trifluoroacetic acid, acetic acid, and ethanolic acetic acid, no reaction occurred and starting material was recovered. It was noteworthy that none of the ring opening product (IIa) was obtained by the reaction of IVa with organic acids. The treatment of IVa with 10% sodium hydroxide afforded IIa as a sole product.

The *para*-substituted compounds on the phenyl group of IVa were treated with acids in order to examine the effect of *para*-substituent to the reaction. These results are sum-

Table II. The Reaction[a] of 3-Benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine with several Acids and Base

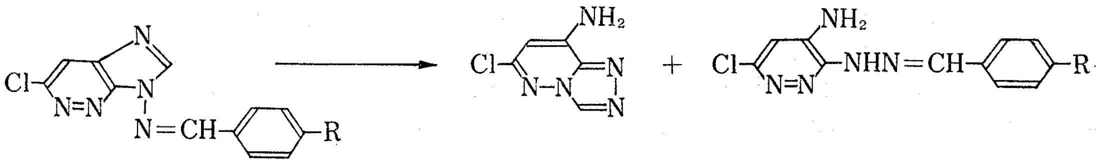


IVa VIII IIa

Prouuct (%)	Reaction No.[b]									
	1	2	3	4	5	6	7	8	9	10
VIII	8	29	53	84	70	91	76	88	40	—
IIa	85	64	10	—	—	—	—	—	—	80

a) Reactions were carried out 0.5 g of IVa and 20 ml of reagent under refluxing for 2 hours.
b) 1; A mixture of 5 ml of 10%HCl and 15 ml of ethanol 2; 1N HCl 3; 0.1N HCl 4; 50%CF_3COOH 5;5 0%CH_3COOH 6; 5%CH_3-COOH 7; A mixture of 3 drops of CH_3COOH and 20 ml of water 8; 45%HCOOH 9; Saturated pivaric acid 10; 10%NaOH

Table III. The Reaction of 3-Ylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (Ib, Ic, and Id) with Acids and Base



IVb, c, d VIII IIb, c, d

R	Product (%)	1N HCl	50%CH_3COOH	50%CF_3COOH	10%NaOH
CH_3	VIII	22	84		
	IIb	73	—		
OCH_3	VIII	14	61		
	IIc	73	—		
NO_2	VIII	—	24	—	—
	IId	85	—	77	50

marized in Table III. As compared with IVa, clear difference was not observed to IVb and IVc. On the other hand, nitro compound (IVd) gave merely the ring opening product (IId) by the reaction with 1 N hydrochloric acid, 50% trifluoroacetic acid, or 10% sodium hydroxide. When 50% acetic acid was used as reagent, the ring isomerization product (VIII) was obtained as minor product and major product (IXd) had a melting point of 260° and elementary analysis was equivalent to $C_{12}H_9O_3N_6Cl$. The infrared (IR) spectrum of IXd showed at 1520 and 1335 cm^{-1} (for nitro group), 1688 cm^{-1} (for carbonyl group) and 3310 cm^{-1} (for secondary amino group). The compound IXd was converted into IId by the reaction with 10% sodium hydroxide. The treatment of IXd with 70% acetic acid afforded VIII but in low yield. These observations suggested that IXd would be 3-(*p*-nitrobenzylidenehydrazino)-4-formamido-6-chloropyridazine.

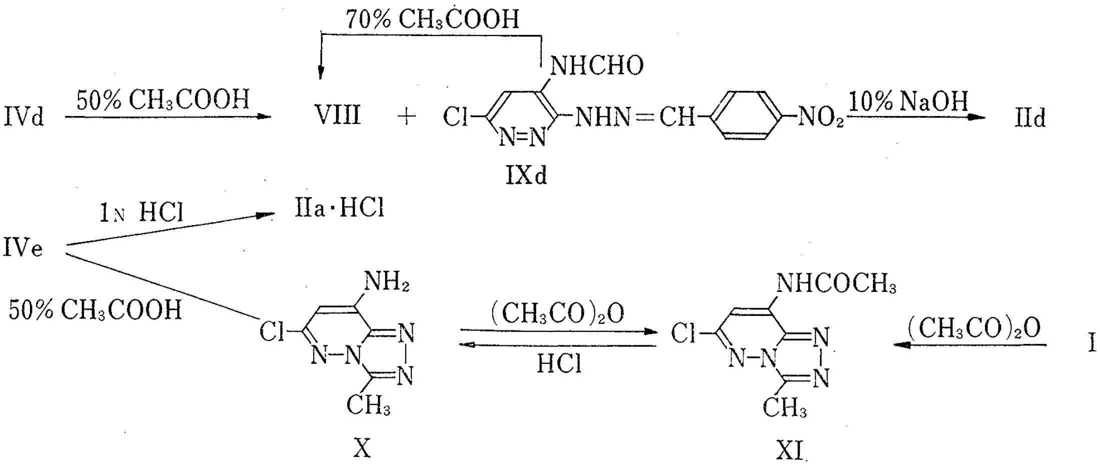


Chart 2

The compound IVe, electron-donor substituent was introduced to C-2 position of IVa, was expected to show less reactivity than IVa against to acids. Actually, no reaction occurred and starting material was recovered by the reaction of IVe with 5% acetic acid. On the other hand, the ring isomerization product (X) was obtained by the treatment of IVe with 50% acetic acid for 7 hr refluxing. The reaction of IVe with 1 N hydrochloric acid gave IIa.

Reactions of 3-Benzylidenehydrazino-4-amino-6-chloropyridazine (II) with Acids

In order to prove reactivity of the C=N bond of benzylidenehydrazino group, IIa was treated with hydrochloric acid, acetic acid, or formic acid. The reaction of IIa with 1 N hydrochloric acid gave a mixture of hydrochlorides of IIa and I in 56% and 25% yield. On the other hand, when organic acids were used, cyclization products were obtained. The compound IIa was converted into 3-phenyl-6-chloro-8-amino-*s*-triazolo[4,5-*b*]pyridazine[4] (IIIa) by the reaction with 20% acetic acid, and to VIII with 90% formic acid, respectively. Similarly, VIII was obtained by the reaction of IId with a mixture of formic acid and acetic anhydride. It was proved that the cleavage of C=N bond of IIa was more difficult than that of IVa by the reaction with acids. As VIII was obtained by the reaction of I with formic acid,[3,4] two routes were assumed to give VIII from IIa (Chart 3). It was suggested that path A was more predominant than path B, because the C=N bond of benzylidenehydrazino group of IIa was difficult to hydrolysis with acids, and the ring closure reaction would be expected to occur prior to hydrolysis under these conditions.

Reaction Mechanism

From the above observations, a reasonable reaction mechanism was proposed as shown Chart 4. It is explained that reactivity of IVe is less than IVa against to acetoxy anion at step a, because IVe has an electron donating methyl group at C-2 position. Step b competes with step c: the step c leading to the ring isomerization product predominates over step b in reaction with organic acids, while step b giving II predominates use of alkaline solution. These steps are so fast that compound C is not isolated. On the other hand, compound C (IXd) was isolated by the reaction of IVd with 50% acetic acid. This observation is explained that attack of carbonium ion is prevented by the nitrogen atom of C=N bond of D, because electron density on the nitrogen atom is diminished by electron-withdrawing effect of nitro group at phenyl group. When hydrochloric acid is used as reagent, it seems that protonation and attack of carbonium ion to the nitrogen atom are competitive reaction. The protonation to the nitrogen atom effects diminution of reactivity of carbonium ion to the nitrogen atom and II is obtained *via* step b. In step d, benzaldehyde was removed which was confirmed as its 2,4-dinitrophenylhydrazone. The ring carbon in the 2 position of IV was rearranged to the 3 position of VIII without scrambling in the reaction with acidic reagents, because IVa, IVb, IVc and IVd were converted to VIII and IVe was then converted to X.

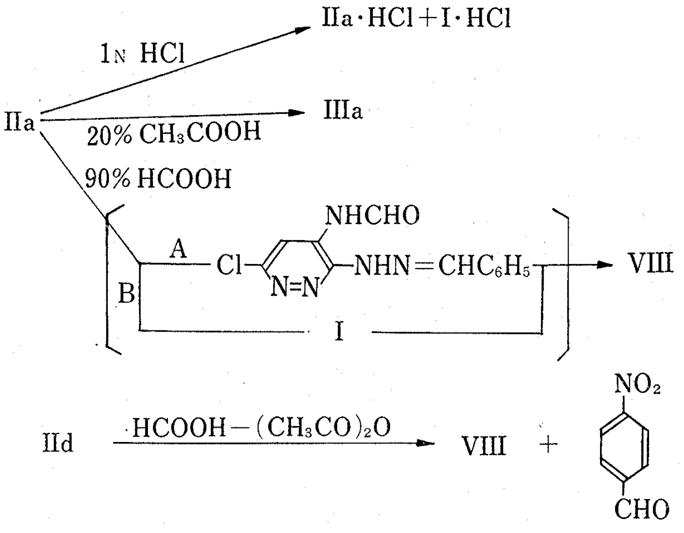


Chart 3

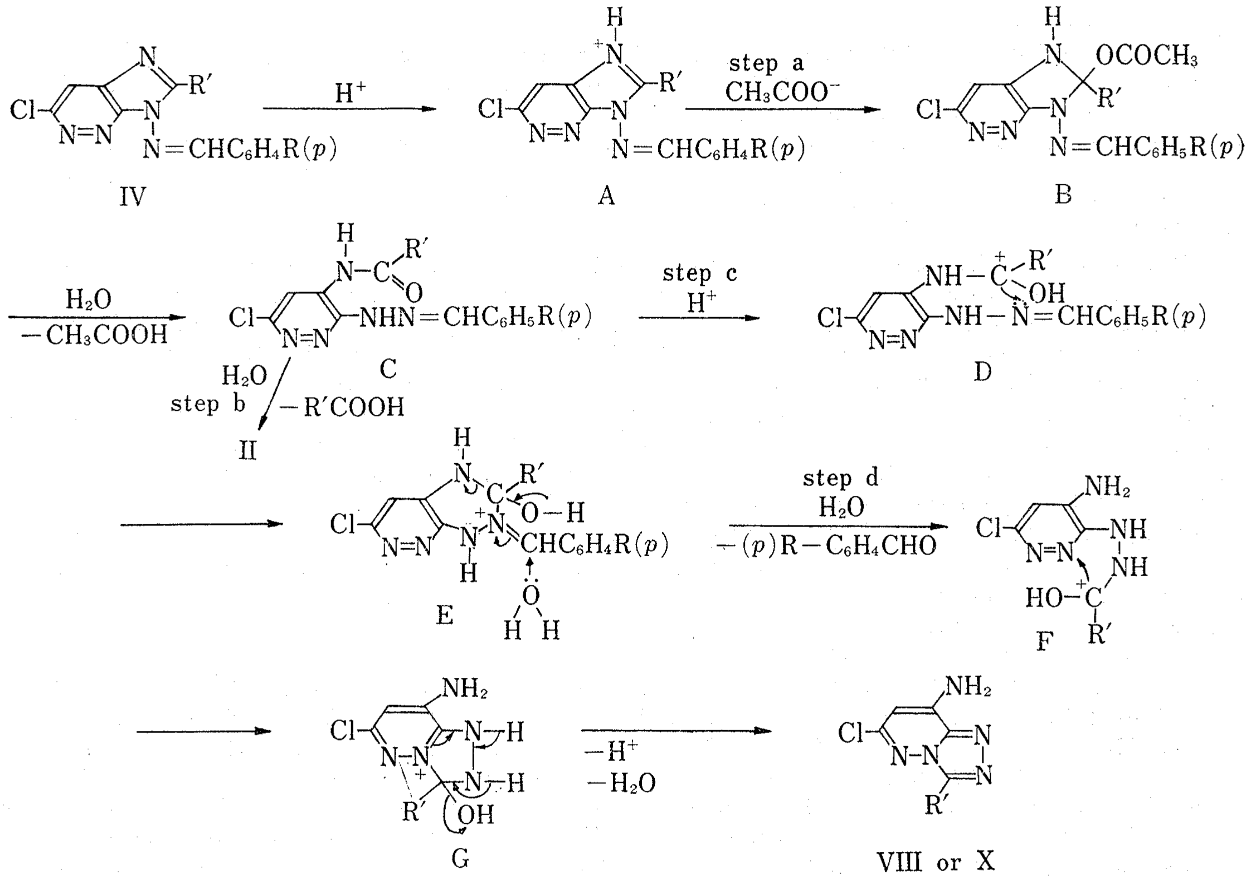


Chart 4

Experimental

General Procedure of 3-Ylidenehydrazino-4-amino-6-chloropyridazine (IIb, IIc, and IId)——A mixture of 0.5 g of I, 1.2 equivalents of *p*-substituted benzaldehyde, 2 drops of acetic acid and 30 ml of ethanol was refluxed for 2 hr (IIb) (IIc, 0.5 hr; IId, 0.25 hr). The reaction mixture was chilled with crushed ice. The precipitated crystals were collected and recrystallized.

General Procedure of 3-(*p*-Substituted Benzylideneamino)-6-chloroimidazo[4,5-*c*]pyridazine (IVb, IVc, and IVd)——A mixture of 0.5 g of II and 10 ml of ethyl orthoformate was refluxed for 3 hr (IVb) (IVc, 2 hr; IVd, 5 hr). After removal of excess ethyl orthoformate *in vacuo*, the residue was recrystallized, if necessary chromatographed over a silica gel column. In cases of IIb and IIc, IIIb, and IIIc were obtained from the mother liquor of recrystallization.

2-Methyl-3-benzylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (IVe)——A mixture of 4 g of IIa and 120 ml of ethyl orthoacetate was refluxed for 4 hr. After evaporation of excess ethyl orthoacetate *in vacuo*, the residue was recrystallized from MeOH to give 2.6 g of IVe. NMR (trifluoroacetic acid) ppm: 8.53 (1H, singlet, H-7), 8.2—7.5 (5H, multiplet, phenyl), 3.27 (3H, singlet, CH_3). From the mother liquor, 0.05 g of IIa was recovered.

Reaction of IIc with $NaNO_2$——To a solution of 1 g of IIc and 45 ml of 30% acetic acid, 0.28 g of $NaNO_2$ was added with stirring and cooling. The mixture was heated at 65° for 15 min. After cooling, the separated brown crystalline mass was filtered and washed with water. The mass was recrystallized from MeOH to give 0.5 g of IIIc as colorless prisms, mp 283—284°. This compound was identified with an authentic sample of IIIc by mixed melting point test and IR comparison.

3-Isopropylidenehydrazino-4-amino-6-chloropyridazine (V)——A mixture of 0.5 g of I, 10 ml of acetone, and 2 drops of acetic acid was refluxed for 2 hr. The reaction mixture was concentrated and the resultant crystals were recrystallized from acetone to give 0.44 g (70%) of V, mp 160—162°. *Anal.* Calcd. for $C_7H_{10}N_5Cl$: C, 42.10; H, 5.02; N, 35.08. Found: C, 42.33; H, 5.20; N, 34.23.

3-Isopropylideneamino-6-chloroimidazo[4,5-*c*]pyridazine (VI)——A mixture of 0.3 g of V and 5 ml of ethyl orthoformate was refluxed for 1 hr. After evaporation of excess ethyl orthoformate, the residue was extracted with MeOH. The extract was concentrated to dryness and the residue was dissolved in AcOEt for chromatography over a neutral alumina column. Evaporation of solvent gave 0.06 g (19%) of VI, colorless needles, mp 152—153°. *Anal.* Calcd. for $C_8H_8N_5Cl$: C, 45.82; H, 3.83; N, 33.41. Found: C, 45.73; H, 3.80; N, 32.93. NMR ($CDCl_3$) ppm: 8.29 (1H, singlet, H-2), 7.88 (1H, singlet, H-7), 2.49 (3H, singlet, CH_3), 2.16 (3H, singlet, CH_3).

Reaction of V with Ethyl Orthoformate and *N*,*N*-Dimethylformamide——A mixture of 0.5 g of V, 0.37 g of ethyl orthoformate, and 3 ml of *N*,*N*-dimethylformamide was refluxed for 1 hr. The reaction mixture was concentrated to dryness *in vacuo* and extracted with hot benzene. The extract was chromatographed on a silica gel column. From benzene elution, 0.25 g of V was recovered. From benzene–acetone (4: 1) elution, 0.1 g of VII was obtained, colorless needles, mp 215—216°. *Anal.* Calcd. for $C_5H_4N_5Cl$: C, 35.39; H, 2.36; N, 41.29. Found: C, 35.51; H, 2.74; N, 40.81. IR ν_{max}^{KBr} cm^{-1}: 3320 and 3220 (NH_2). UV λ_{max}^{EtOH} nm (log ε): 262 (3.97), 301 (3.82).

Reactions of IV with Acids——a) A mixture of 0.5 g of IV and 20 ml of acidic solution was refluxed for 2 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue was recrystallized from MeOH to give colorless needles of VIII. Reagent of 2,4-dinitrophenylhydrazine was added to the distillate, the separated orange crystals were collected, mp 253—256°. This compounds was identified with an authentic sample of benzylidene 2,4-dinitrophenylhydrazone by mixed melting point test and IR comparison.

b) A mixture of 0.5 g of IV and 20 ml of 1 N HCl was refluxed for 2 hr. The separated crystals were collected and recrystallized from MeOH to give II·HCl. The filtrate was concentrated to dryness *in vacuo* and the residue was recrystallized from MeOH to give VIII. 2,4-Dinitrophenylhydrazone was obtained from the distillate by the same treatment described above a).

Hydrolysis of IVb, IVc, and IVd with 10% NaOH——To a suspended mixture of 0.3 g of IV and 40 ml of MeOH, 1 ml of 10% NaOH was added. The mixture was stirred overnight, the separated crystalline mass was collected (if crystals were not separated, the reaction mixture was neutrallized with acetic acid and then concentrated to dryness *in vacuo*). The crystalline mass or the residue was recrystallized. The corresponding II was obtained in 50—80% yield.

Reaction of IVd with 50% Acetic Acid——A mixture of 0.5 g of IVd and 20 ml of 50% acetic acid was refluxed for 2.5 hr. The separated crystals were filtered and recrystallized from pyridine to give 0.35 g (65%) of IXd as orange needles, mp 260—262°. *Anal.* Calcd. for $C_{12}H_9O_3N_6Cl$: C, 44.94; H, 2.82; N, 25.58. Found: C, 45.26; H, 2.87; N, 25.58. The filtrate was concentrated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 0.07 g (24%) of VIII as colorless needles, mp 276—277° (decomp.). This compound was identified with an authentic sample of VIII by mixed melting point test and IR comparison.

Reaction of IXd with 10% NaOH——A mixture of 0.2 g of IXd and 3 ml of 10% NaOH was refluxed for 10 min. After cooling with crushed ice, the separated crystals were collected and washed with water, then recrystallized from pyridine to give 0.06 g of IId, mp 262—264°. This compound was identified with an authentic sample of IId by IR comparison.

Reaction of IXd with 70% Acetic Acid——A mixture of 0.01 g of IXd and 17 ml of 70% acetic acid was refluxed for 13 hr. The reaction mixture was concentrated to dryness *in vacuo*. The residue was recrystallized from water to give 0.015 g of VIII, mp 276—277° (decomp.). This compound was identified with an authentic sample of VIII by mixed melting point test and IR comparison.

Hydrolysis of IVe with 1 N HCl——A suspended mixture of 0.5 g of IVe and 15 ml of 1 N HCl was refluxed for 2 hr. During refluxing of the mixture, needles crystals were changed into powdered crystals. The powdered crystalline mass was collected and recrystallized from MeOH to give 0.15 g of IIa·HCl, yellow cubes, mp 263—264°. *Anal.* Calcd. for $C_{11}H_{10}N_5Cl \cdot HCl$: C, 46.49; H, 3.90. Found: C, 46.60; H, 4.10.

Reaction of IVe with 50% Acetic Acid——A mixture of 0.4 g of IVe and 16 ml of 50% acetic acid was refluxed for 7 hr. After cooling, the separated crystalline mass was collected and recrystallized from MeOH to give 0.18 g of X as pale yellow prisms, mp 229—230°. *Anal.* Calcd. for $C_6H_6N_5Cl \cdot H_2O$: C, 35.75; H, 4.00; N, 34.74. Found: C, 36.04; H, 4.16; N, 34.59. IR ν_{max}^{KBr} cm^{-1}: 3370 and 3220 (NH_2). UV λ_{max}^{EtOH} nm (log ε): 221 (4.38), 240 (3.97), 261 (shoulder, 3.55), 275 (sh., 3.55), 299 (sh., 3.98), 306 (4.04), 316 (sh., 3.91). NMR (dimethylsulfoxide-d_6) ppm: 7.8 (2H, broad, disappear by addition of D_2O, NH_2), 6.10 (1H, singlet, H-7), 2.60 (3H, singlet, CH_3). This compound was obtained by the hydrolysis of XI with 10% HCl followed by neutralization with $NaHCO_3$.

3-Methyl-6-chloroy-8-acetamido-*s*-triazolo[4,5-*b*]pyridazine (XI)——a) A mixture of 0.4 g of I and 8 ml of acetic anhydride was refluxed for 2 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue was recrystallized from MeOH to give 0.45 g of XI as colorless prisms, mp 230—231°. *Anal.* Calcd. for $C_8H_8ON_5Cl$: C, 42.59; H, 3.58; N, 31.04. Found: C, 42.85; H, 3.78; N, 30.63. NMR (trifluoroacetic acid) ppm: 8.54 (1H, singlet, H-7), 3.21 (3H, singlet, CH_3CO), 2.69 (3H, singlet, CH_3).

b) A mixture of 20 mg of X and 3 ml of acetic anhydride was refluxed for 4 hr. The reaction mixture was concentrated to dryness *in vacuo* and the residue was recrystallized from MeOH to give XI as colorless prisms, mp 230—231°. This compound was identified with the sample obtained above experiment, by mixed melting point test and IR comparison.

Reaction of IIa with Acids——a) 1 N HCl: A mixture of 0.1 g of IIa and 3 ml of 1 N HCl was refluxed for 2 hr. The precipitated crystals were collected and recrystallized from MeOH to give 0.06 g of IIa·HCl, mp 265°. This compound was identified with an authentic sample of IIa·HCl by IR comparison. The filtrate was concentrated to dryness *in vacuo*. The residue was recrystallized from MeOH to give 0.02 g of I·HCl, mp 245°. This compound was identified with an authentic sample of I·HCl by IR comparison.

b) 20% Acetic Acid : *cf.* reference 3).

c) 90% Formic Acid : A mixture of 0.1 g of IIa and 3 ml of 90% formic acid was refluxed for 2 hr. After evaporation of excess formic acid *in vacuo*, the residue was recrystallized from water to give 0.06 g of VIII, mp 274—275° (decomp.). This compound was identified with an authentic sample of VIII by IR comparison.

Reaction of IId with a Mixture of Formic Acid and Acetic Anhydroride——A mixture of 0.3 g of IId, 5 ml of formic acid, and 1 ml of acetic anhydride was heated at 85—95° for 9 hr. To the reaction mixture, 5 ml of EtOH was added, and concentrated to dryness *in vacuo*. The residue was extracted with benzene. The insoluble materials were recrystallized from water to give 0.05 g of VIII as colorless needles, mp 275—276° (decomp.). This compound was identified with an authentic sample of VIII by IR comparison. The benzene extract were chromatographed on a silica gel column, 0.01 g of *p*-nitrobenzaldehyde was obtained.

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